PATENT ABSTRACTS OF JAPAN

(11)Publication number : 09-087164
(43)Date of publication of application : 31.03.1997

(51)Int.Cl. A61K 7/48
A61K 7/00
A61K 35/78
A61K 35/78
A61K 35/78
C12N 9/99

(21)Application number : 08-203118
(22)Date of filing : 12.07.1996

(71)Applicant : SHISEIDO CO LTD
(72)Inventor : NAKAYAMA TAIICHI
SUZUKI YUMIKO
YOKOGAWA YOSHIHIRO
TANAKA NAOMI
YAGI EIICHIRO
SAKAMOTO OKIHIKO

(30)Priority
Priority number : 07200467 Priority date : 13.07.1995 Priority country : JP

(54) SKIN PREPARATION FOR EXTERNAL USE

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a skin preparation for external use suitable for lightening skin and preventing aging, excellent in inhibitory action on tyrosinase activity and promoting action on collagen production.
SOLUTION: This skin preparation for external use contains 0.0005–20wt.%, preferably 0.001–10wt.% calculated as a dried substance of an extract of a plant of Pule and/or Uret-uret growing in a dry meadow, pasture, etc., especially in Indonesia. The extract of Pule and/or Uret-uret is obtained by immersing leaves, stems, flowers, bark, seeds. fruits, the whole plant of Pule and/or Uret- uret in an extractive solvent (e.g. solvent) or heating under reflux, filtering and concentrating. The extract is properly mixed with conventional additives and can be prepared into an ointment, cream, milky lotion, pack, bathing agent, etc. The skin preparation for external use has excellent effects on pigmentation after suntan, stain, freckles, lightening such as chloasma and lightening skin, maintains lively skin free from wrinkle and slack, etc., prevents skin aging and can retain young skin.

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1]Skin external preparations blending a kind chosen from an extract of the following vegetation, or two sorts or more.
(1) Pre (Pule, scientific name:Alstonia scholaris)
(2) the Ule -**** (Uret-uret and scientific name:Helicteres ixora L.)
[Claim 2]The skin external preparations according to claim 1 which are tyrosinase inhibitor.
[Claim 3]The skin external preparations according to claim 1 which are an anti aging agent.
[Claim 4]The skin external preparations according to claim 3 which are a promoter for producing collagen.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]This invention has the effect which has tyrosinase activity inhibitory action effective in the prevention and the improvement of pigmentation, a stain, a freckle, a chloasma, etc. after suntan, and was excellent in whitening of the skin by blending the extract of specific vegetation, and. It is related with the skin external preparations which can raise the collagen production ability of the skin and can prevent aging of the skin.
[0002]
[Description of the Prior Art]Although there is also a question in part about developmental mechanisms, such as a stain of the skin, generally, a stimulus of the ultraviolet rays from the abnormalities and daylight of hormone becomes a cause, a melanin is formed, and it is thought that this carries out unusual deposition into the skin. The melanin which this melanin leading to coloring of the skin was produced in the melanin generation granulation (melanosome) in the melanocyte (melanocyte) between epidermis and dermis, and was generated is diffused to a contiguity cell by osmosis operation. The biochemical reaction in this melanocyte is presumed to be the following.
[0003]That is, the process in which this changes with enzymatic or nonenzymatic oxidation to black melanin through red dyes and colorless coloring matter by tyrosine which is an essential amino acid serving as a dopa quinone by operation of an enzyme tyrosinase is a generation process of a melanin. Therefore, it is important for control of melanin generation to inhibit an operation of the tyrosinase which is the 1st step of a reaction.
[0004]however -- if the compound which inhibits a tyrosinase action removes hydroquinone -- since the manifestation of the effect is very slow -- skin color matter -- a self-possessed improvement effect is not enough. On the other hand, although hydroquinone is accepted [the effect] once, since it has sensitization, generally use is restricted. Then, in order to raise the safety, the trial (JP,58-154507,A) used as monoester, alkyl monoether, etc. of higher fatty acid is made, but. Since ester species is decomposed by hydrolase in the living body, what is hard to be called safety and is fully satisfied with the field of safety of ether is not necessarily obtained.
[0005]On the other hand, if research on aging is advanced in recent years and it sees on a macro target as a cause of skin aging, aging will be an important factor, and desiccation, oxidation, the influence by sunlight (ultraviolet rays), etc. have been further mentioned as a direct factor in connection with skin aging. Although reduction of mucopolysaccharides including the crosslinking reaction of collagen and hyaluronic acid, damage to the cell by ultraviolet rays, etc. are known as a concrete phenomenon of skin aging, It became clear [that aging of the skin cannot fully be prevented only by blending biochemistry products and synthetic macromolecule products, such as a mucopolysaccharide and collagen, and striving for moisture maintenance like the conventional cosmetics, either].
[0006]Then, by working on the fibroblast in the skin and promoting the biosynthesis of collagen which is one of the ingredients with important dermis, aging of the skin could be prevented and a promoter for producing collagen which is moreover satisfactory also in respect of safety was desired. As an ingredient which has such a collagen production promotion operation, The

zymolysis thing produced by processing with an enzyme the alkaline extraction liquid of the hypoallergic rice which processed and obtained rice with the proteolytic enzyme beforehand which applicants for this patent found out is known (Japanese Patent Application No. No. 243463 [seven to], Japanese Patent Application No. No. 97654 [eight to]). And further substance that has the outstanding collagen production promotion ability was desired.

[0007]

[Means for Solving the Problem]Then, a result in which this invention persons investigated tyrosinase activity inhibition ability and collagen production promotion ability about various substances large as what solves these problems, It finds out having tyrosinase activity inhibitory action and a collagen production promotion operation excellent in a specific plant extract, and came to complete this invention. A report of tyrosinase activity inhibitory action of an extract of these vegetation etc. which carry out a postscript is unprecedented, and, as for application to ** and skin external preparations, application to a whitening agent and an anti aging agent is not known at all. This invention persons came to complete this invention based on the above-mentioned knowledge.

[0008]That is, this invention is skin external preparations blending a kind chosen from an extract of the following vegetation, or two sorts or more.

(1) Pre (Pule, scientific name:Alstonia scholaris)

(2) Ule -**** (Uret-uret and scientific name:Helicteres ixora L.)

[0009]Skin external preparations of this invention make it suitable to be tyrosinase inhibitor or an anti aging agent, and make it suitable to be a promoter for producing collagen also in it about an anti aging agent.

[0010]Hereafter, composition of this invention is explained in full detail. Especially the vegetation used for this invention is vegetation which grows in a dry prairie in Indonesia, grass, etc. After an extract used for this invention immerses or flows back [heating] a leaf of the above-mentioned vegetation, a stem, a flower, a bark, a seed or fruits, the vegetable entire plant, etc. with an extracting solvent, it is filtered, condensed and obtained. if an extracting solvent used for this invention is a solvent usually used for extraction, it is [anything] good and especially independent in organic solvents, such as alcohols, such as methanol and ethanol, hydrous alcohols, acetone, and acetic acid ethyl ester, -- or it can combine and use.

[0011]Loadings of an extract of vegetation in this invention are 0.001 to 10.0 % of the weight preferably 0.0005 to 20.0% of the weight as a dry matter among the external-preparations whole quantity. Since pharmaceutical-preparation-izing is difficult when an effect referred to as being less than 0.0005 % of the weight by this invention is not fully demonstrated but exceeds 20.0 % of the weight, it is not desirable. Even if it blends 10.0% of the weight or more, improvement in so big an effect is not found.

[0012]An ingredient usually used for skin external preparations of this invention at skin external preparations, such as cosmetics and drugs, in addition to the above-mentioned essential ingredient, For example, other whitening agents, a moisturizer, an antioxidant, an oily component, an ultraviolet ray absorbent, a surface-active agent, a thickener, alcohols, a powder constituent, a coloring material, an aqueous ingredient, water, various skin nutrients, etc. can be blended suitably if needed.

[0013]In addition, disodium edetate, edetate trisodium, sodium acid citrate, Sequestering agents, such as sodium polyphosphate, sodium metaphosphate, and gluconic acid, Caffeine, tannin, verapamil, tranexamic acid, and its derivative, A glycyrrhiza extract, glove lysine, a hot water extract of fruits of a Chinese quince, various crude drugs, Drugs, such as tocopherol acetate, glycyrrhizic acid and its derivative, or its salt, Sugars, such as other whitening agents, such as vitamin C, ascorbic acid magnesium phosphate, ascorbic acid glucoside, arbutin, and kojic acid, glucose, fructose, mannose, sucrose, and trehalose, etc. can be blended suitably.

[0014]As long as skin external preparations of this invention use ointment, cream, a milky lotion, a lotion, a pack, baths, etc. for skin external preparations conventionally, for example, any may be sufficient as them, and a pharmaceutical form in particular does not ask.

[0015]

[Example]Next, an example explains this invention still in detail. Thereby, this invention is not

limited. Loadings are weight %. In advance of an example, the test method about the ** tyrosinase activity inhibition effect of the plant extract of this invention and ** collagen production facilitatory effect and its result are explained.

[0016]** Preparation of a tyrosinase activity inhibition effect 1. sample [0017](1) a pre (Pule) extract -- pre (Pule) bark partial 50g was immersed in ethanol for one week at the room temperature, the extract was condensed, and the ethanol extract 1.1g was obtained. This extract was melted 1% in DMSO, this solution was diluted, concentration was adjusted, and the following experiments were conducted using this.

[0018](2) 50 g of fruit portions of the Ule -**** (Uret-uret) extract Ule -**** (Uret-uret) were immersed in ethanol for one week at the room temperature, the extract was condensed, and the ethanol extract 0.2g was obtained. This extract was melted 1% in DMSO, this solution was diluted, concentration was adjusted, and the following experiments were conducted using this.

[0019]2. It is (1) as a result of [its] a test method. B16 melanoma cultured cell of the cell cultivation mouse derived was used. It cultivated within CO_2 incubator (95% air, 5% carbon dioxide) and under 37 ** conditions in the MEM culture medium which contains FBS and theophylline (0.09mg/(ml)) 10%. 24 hours after culture, the sample solution was added so that it might become 10^{-2} - 10^{-5} weight % with final concentration (extraction dry matter conversion concentration), culture was continued for three more days, and the tyrosinase activity inhibition effect was measured by the following methods.

[0020](2) before measurement measurement of tyrosinase activity -- a well -- remove an inner culture medium and wash it twice by PBS100microl. each -- PBS which contains 1% Triton X (a loam and Haas trade name, a surface-active agent) of 45microl in a well is added. The plate was vibrated for 1 minute, the cell membrane was often destroyed, the absorbance of 475 nm was measured with the microplate leader, and this was made into the absorbance of zero minute. Then, the L-DOPA solution of 10mM of 5microl was added quickly, and it moved to a 37 ** incubator, and was made to react for 60 minutes. The plate was vibrated for 1 minute and the absorbance (475 nm) of 60 minutes was measured. The rate of said absorption difference of the plant extract addition sample to the absorption difference of zero minute in the case of the sample (control) which has not added the plant extract, and 60 minutes was made into the rate of tyrosinase activity (%). The result is shown in Table 1. The examination same also about the ethanol extract of Schizonepetae herba (the Lamiaceae dead nettle subfamily) in which it is known as a reference example that tyrosinase activity inhibitory action already occurs as the above was done. The result is collectively shown in Table 1. - means among front that a significant difference was not accepted by less than 5% of percentage of risk compared with control.

[0021]

[Table 1]

---. Examination The rate of tyrosinase activity (%). ---. ---. Concentration (% of the weight) $10^{-5}10^{-4}10^{-3}10^{-2}$. --- pre extract 53 - - - Ule -**** extract - - 71 67 Schizonepetae herba extract - - - 55---

[0022]** Each sample was prepared like the case in the preparation tyrosinase activity inhibition effect of a collagen production facilitatory effect 1. sample.

[0023]2. The Homo sapiens dermal fibroblast was wound around cell cultivation and the measurement 96 hole petri dish of a collagen production promotion operation 20,000, and after cultivating by RITC80-7 which contains FBS 10% for 48 hours, it exchanged for the culture medium which contained FBS 0.5%, the plant extract which dissolved in DMSO was added, and it cultivated for further 48 hours. DMSO was added so that it might become 1/200 (it is 5microl to 1 ml of culture media). Extract concentration was made into 10^{-5} - 10^{-2} weight %. The after-culture culture medium was extracted and it used for measurement of collagen. The amount of DNAs in a petri dish was measured, and it was considered as the index of the cell number. Measurement of the amount of DNAs was performed with the fluorometry which used H33258.

Although cytotoxicity was accepted by each by 10^{-2} weight % about the extract of each vegetation, toxicity was not accepted in 10^{-3} weight %. . Then, measured the I-beam procollagen C terminal peptide (Procollagen type I carboxyterminal propeptide:PIP) which a culture Homo sapiens dermal fibroblast produces by the ELISA method. The amount of PIP of the plant extract addition sample of 10^{-3} weight % concentration when the amount of PIP per DNA of the sample (control) which has not added the plant extract is set to 100 was measured, and it was considered as the collagen production promotion rate (%). The result is shown in Table 2. The examination same also about the solvent extraction thing of a water caltrop in which it is known as a reference example that there is already a collagen production promotion operation as the above was done. The result is collectively shown in Table 2.

[0024]

[Table 2]

----------. Examination Collagen production facilitatory effect (%) ---------- ---------- pre extract 176.6 The Ule -**** extract 123.9 Water caltrop extract 124.1----------

[0025]Below, the example of combination of the skin external preparations by this invention of various pharmaceutical forms is explained as an example.

[0026]Example 1 Cream (formula)

stearic acid 5.0 weight % stearyl alcohol . 4.0 isopropyl myristate 18.0 glycerin monostearin acid ester 3.0 propylene glycol 10.0 pre methanolic extract 0.01 caustic potash 0.2 sodium hydrogen sulfite 0.01 antiseptic Optimum dose perfume . It is ion exchange water in proper quantity.

Propylene glycol, a pre methanolic extract, and caustic potash are added to residual (process) ion exchange water, and it dissolves, and it heats and keeps at 70 ** (aqueous phase). Other ingredients are mixed, heating fusion is carried out, and it keeps at 70 ** (oil phase). Since an oil phase is gradually added to the aqueous phase and it all finishes adding it to it, it maintains at the temperature for a while, and a reaction is made to cause. Then, by a homomixer, it emulsifies uniformly and cools to 30 ** with stirring well.

[0027]example 2 cream (formula)

stearic acid 2.0 weight % stearyl alcohol . 7.0 hydrogenated lanolin 2.0 squalane . 5.0 2-octyldodecyl alcohol . 6.0 polyoxyethylene (25 mol) cetyl alcohol ether 3.0 glycerin monostearin acid ester 2.0 propylene glycol 5.0 ****- Ule ethanol extract 0.05 sodium hydrogen sulfite . 0.03 Ethylparaben 0.3 Perfume Optimum dose ion exchange water Propylene glycol is added to residual (process) ion exchange water, and it heats, and keeps at 70 ** (aqueous phase). Other ingredients are mixed, heating fusion is carried out, and it keeps at 70 ** (oil phase). After adding an oil phase to the aqueous phase, performing preliminary emulsification and emulsifying uniformly by a homomixer, it cools to 30 ** with stirring well.

[0028]example 3 cream (formula)

hard paraffin 5.0 weight % yellow bees wax . 10.0 vaseline 15.0 liquid paraffins . 41.0 glycerin monostearin acid ester . 2.0 polyoxyethylene (20 mol) sorbitan mono- laurate ester 2.0 soap powder 0.1 borax 0.2 -- pre acetone extract 0.05 ****- Ule ethanol extract 0.05 sodium hydrogen sulfite . 0.03 ethylparabens 0.3 Perfume Optimum dose Ion exchange water The heating and dissolving of soap powder and the borax are added and carried out to residual (process) ion exchange water, and it keeps at 70 ** (aqueous phase). Other ingredients are mixed, heating fusion is carried out, and it keeps at 70 ** (oil phase). In addition, it reacts gradually, stirring an oil phase to the aqueous phase. After ending reaction, by a homomixer, it emulsifies uniformly and cools with the sufficient emulsification back to 30 ** with stirring.

[0029]Example 4 Milky lotion (formula)

stearic acid 2.5 weight % cetyl alcohol . 1.5 vaseline 5.0 liquid paraffins . 10.0 Polyoxyethylene (10 mol) monooleate 0.05 (B.F.Goodrich trade name: Carbopol 941) 2.0 Polyethylene glycol 1500 3.0 Triethanolamine 1.0 Carboxyvinyl polymer Chemical company)

Pre ethyl acetate ester extract 0.01 sodium hydrogen sulfite 0.01 Ethylparaben 0.3 Perfume Optimum dose Ion exchange water A carboxyvinyl polymer is dissolved in the ion exchange water of a residual (process) small quantity (A phase). The heating and dissolving of the polyethylene

glycol 1500 and the triethanolamine are added and carried out to the remaining ion exchange water, and it keeps at 70 ** (aqueous phase). Other ingredients are mixed, heating fusion is carried out, and it keeps at 70 ** (oil phase). An oil phase is added to the aqueous phase, preliminary emulsification is performed and an A phase is added, and by a homomixer, uniform emulsification is carried out and it cools with the sufficient emulsification back to 30 ** with stirring.

[0030]Example 5 Milky lotion (formula)

Microcrystallin wax 1.0 Weight % . dense low 2.0 lanolin 20.0 liquid paraffins . 10.0 Squalane 5.0 Sorbitan sesquioleate 4.0 Polyoxyethylene (20 mol) sorbitan monooleate ether 1.0 propylene glycol 7.0 ****- Ule acetone extract 10.0. Sodium hydrogen sulfite 0.01 Ethylparaben 0.3 Perfume Optimum dose Ion exchange water Propylene glycol is added to residual (process) ion exchange water, and it heats, and keeps at 70 ** (aqueous phase). Other ingredients are mixed, heating fusion is carried out, and it keeps at 70 ** (oil phase). The aqueous phase is gradually added to this, stirring an oil phase, and it emulsifies uniformly by a homomixer. It cools with the sufficient emulsification back to 30 ** with stirring.

[0031]Example 6 Jelly (formula)

95% ethyl alcohol 10.0 Weight % . Dipropylene glycol 15.0 Polyoxyethylene (50 mol) oleyl alcohol ether 2.0 Carboxyvinyl polymer 1.0 (trade name: Carbopol 940, B.F.Goodrich Chemical company) Caustic alkali of sodium 0.15 L-arginine 0.1. Pre 50% ethanol solution extract 7.02-hydroxy-4-methoxybenzophenone sulfone sodium 0.05 Ethylenediamine tetra acetate, 3 sodium, and 2 water 0.05 Methylparaben 0.2. Perfume Optimum dose ion exchange water Carbopol 940 is uniformly dissolved in residual (process) ion exchange water, and on the other hand, an ethanol solution extract and polyoxyethylene (50 mol) oleyl alcohol ether are dissolved in ethanol pre 50% 95%, and it adds to the aqueous phase. Subsequently, after adding other ingredients, caustic alkali of sodium and L-arginine are made to neutralize, and it thickens.

[0032]Example 7 Essence (formula)

(A phase)

Ethyl alcohol (95%) 10.0 Weight % polyoxyethylene (20 mol) octyldodecanol 1.0 Pantothenyl ethyl ether 0.1 ****- Ule methanolic extract 1.5 Methylparaben 0.15 (B phase)

Potassium hydrate 0.1 (C phase)

Glycerin 5.0 Dipropylene glycol 10.0 sodium hydrogen sulfite 0.03 carboxyvinyl polymer 0.2 (trade name: Carbopol 940, B.F.Goodrich Chemicalcompany)

Purified water A residual (process) A phase and C phase are dissolved in homogeneity, respectively, and an A phase is added and solubilized to C phase. Subsequently, restoration is performed after adding a B phase.

[0033]example 8 pack (formula)

(A phase)

Dipropylene glycol 5.0 Weight % polyoxyethylene (60 mol) hydrogenated castor oil 5.0 (B phase) Pre methanolic extract 0.01 olive oil 5.0 tocopherol acetate 0.2 Ethylparaben 0.2 Perfume 0.2 (C phase)

Sodium hydrogen sulfite 0.03 Polyvinyl alcohol 13.0 (the degree 90 of saponification, the degree of polymerization 2,000)

Ethanol 7.0 Purified water A residual (process) A phase, a B phase, and C phase are dissolved in homogeneity, respectively, and a B phase is added and solubilized to an A phase. Subsequently, restoration is performed after adding this to C phase.

[0034]Example 9 cake makeup (formula)

talc 43.1 weight % kaolin 15.0 sericites . 10.0 flowers of zinc 7.0 titanium dioxides 3.8 Synthetic Ochre . 2.9 black iron oxide 0.2 squalane 8.0 isostearic acid 4.0 monooleic acid POE sorbitan 3.0 octanoic-acid isocetyl 2.0 ****- Ule ethanol extract 1.0 antiseptic Optimum dose perfume The powder constituent of optimum dose (process) talc - black iron oxide. It mixes enough with a blender, and it fills up and molds into a container, after being easy to season this with the oily component of squalane - octanoic acid isocetyl, a ****- Ule ethanol extract, an antiseptic, and perfume and kneading them to it.

[0035]Example 10 Emulsified type foundation (cream type)

(Formula)
(Granular material part)
Titanium dioxide 10.3 Weight % sericite 5.4 Kaolin 3.0 Synthetic Ochre 0.8 Red ocher 0.3 Black iron oxide 0.2 (oil phase)
Decamethyl cyclopentasiloxane 11.5 liquid paraffins 4.5 Polyoxyethylene denaturation dimethylpolysiloxane 4.0 (aqueous phase)
Purified water 50.0 1,3-butylene glycol 4.5 Pre ethanol extract 1.5 Sorbitan sesquioleate 3.0 Antiseptic Optimum dose Perfume The granular material part which fully carried out preferential grinding of the optimum dose (process) aqueous phase after heating stirring is added, and homomixer processing is carried out. After adding the oil phase which carried out heating mixing and carrying out homomixer processing, stirring, perfume is added and it cools to a room temperature.
[0036]
[Effect of the Invention]As explained above, the skin external preparations of this invention have the outstanding tyrosinase activity inhibitory action and collagen production promotion operation. It has the effect excellent in light-color-izing of the pigmentation, the stain, freckle, chloasma, etc. after suntan, and whitening, and production of collagen can be promoted, the elastic skin without wrinkles or sag can be maintained, aging of the skin can be prevented and the state of a youthful skin can be maintained.

[Translation done.]